

PATENT SPECIFICATION

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(54) HYDROGELS

(71) We, NATIONAL RESEARCH DEVELOPMENT CORPORATION, a British Corporation established by Statute, of Kingsgate House, 66-74 Victoria Street, London, S.W.1, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

10 This invention relates to polymeric materials suitable for use in bio-medical applications and in the form of a hydrogel.

In our Complete Specification 1500692 we have described and claimed a polymeric material suitable for use in bio-medical applications which comprises a hydrophilic copolymer containing units derived from a hydroxyl substituted unsaturated aliphatic compound units derived from an amide of an unsaturated aliphatic carboxylic acid and units derived from an unsaturated aliphatic carboxylic acid or a mono-ester thereof, the copolymer being capable of absorbing water. The term "hydroxyl-substituted unsaturated aliphatic compound" as used therein includes such compounds wholly or partly replaced by a *N*-vinyl lactam, for example *N*-vinyl pyrrolidone.

According to the present invention there is provided a polymeric material suitable for use in bio-medical applications and in the form of a hydrogel containing units derived from (i) a hydroxyl substituted olefin and/or a hydroxyl substituted unsaturated aliphatic ester; (ii) an amide of an unsaturated aliphatic carboxylic acid; and (iii) an unsaturated lactam, the hydrogel having an equilibrium water content of at least 72% by weight.

The invention also provides a process for the preparation of such a polymeric material suitable for use in bio-medical applications

which comprises copolymerising a hydroxyl substituted olefin and/or a hydroxyl-substituted unsaturated aliphatic ester, an amide of an unsaturated aliphatic carboxylic acid, and an unsaturated lactam.

Component (i) may be a hydroxyl substituted olefin such as 3-methyl-3-buten-1-ol, 3-methyl-3-buten-2-ol, 2-methyl-1-penten-3-ol, 2-methyl-4-penten-2-ol, and 4-methyl-1-penten-3-ol, but is preferably a hydroxyl substituted unsaturated aliphatic ester, more particularly an ester of acrylic or methacrylic acid and a dihydric alcohol, for example, hydroxy methyl acrylate, hydroxy ethyl acrylate, hydroxy propyl acrylate, hydroxy methyl methacrylate, hydroxy ethyl methacrylate, and hydroxy propyl methacrylate. Excellent results have been obtained with hydroxy propyl acrylate. Mixtures of any of the above monomers may be used.

The amide of an unsaturated aliphatic carboxylic acid is preferably an amide of acrylic acid or methacrylic acid, for example acrylamide, an ethacrylamide, or diacetone acrylamide.

The unsaturated lactam may be an *N*-vinyl lactam such as *N*-vinyl pyrrolid-2-one and alkyl substituted derivatives thereof, for example *N*-vinyl-5-methyl pyrrolid-2-one, *N*-vinyl-5-ethyl pyrrolid-2-one, *N*-vinyl-5, 5-dimethyl pyrrolid-2-one, *N*-vinyl-5, 5-diethyl pyrrolid-2-one, and *N*-vinyl-5-methyl-5-ethyl pyrrolid-2-one. Excellent results have been obtained with *N*-vinyl pyrrolid-2-one.

The hydrogel may also comprise (iv) an unsaturated aliphatic carboxylic acid, such as methacrylic acid or a higher homologue thereof, itaconic acid, mesaconic acid, citraconic acid and aconitic acid; and/or a monoester thereof. Excellent results have been

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obtained with methacrylic acid which is the preferred acid. It is usually not desirable to use acrylic acid as the unsaturated aliphatic carboxylic acid, because copolymers of acrylic acid tend to behave as polyelectrolytes and their water content may vary with the pH. The monoester of an unsaturated aliphatic carboxylic acid is preferably an ester of acrylic or methacrylic acid, for example an alkyl or alkoxy alkyl ester such as a methyl, ethyl, propyl, butyl or ethoxyethyl ester.

For many bio-medical applications, it is desirable to use a polymeric material in the form of a hydrogel, having a water content that is as high as possible, consistent with the material having adequate mechanical strength. It is usually found that gels containing at least 72% of water by weight may be obtained using copolymers in which there is from 5 to 70 mole %, and particularly from 5 to 45 mole % of component (ii) and from 5 to 50 mole % of component (iii) and (iv) (where present), percentages being relative to the total copolymer.

It is found that the presence of the monoester of an unsaturated aliphatic acid in the copolymer permits the use of larger quantities of the amide in bulk polymerisation systems, producing on hydration copolymers having a higher water content. Copolymers including a monoester of an unsaturated aliphatic carboxylic can have a high water content and may be lathe cut into contact lenses. Preferred copolymers including a monoester may comprise from 5 to 50 mole % of the monoester of an unsaturated aliphatic acid.

In general it is found that increasing the length of an alkyl group in any individual monomeric component decreases the water content of the copolymer on hydration. For example, using a glycol acrylate as the hydroxyl substituted unsaturated aliphatic compound, it is found that acrylates give 6% more water up-take than methacrylates, which in turn give more water up-take than higher homologues.

In addition to the four components specified, the copolymer may comprise small quantities, usually not more than 20 mole % of other monomers which may improve the physical properties of the copolymer for particular applications. For example, monomers having antibacterial activity may be included, and also monomers which affect the surface properties of the copolymer.

In order to obtain the desired ratio of monomeric components in the copolymer, it is sometimes found necessary to vary the feed ratio according to the polymerisation technique adopted.

The polymerisation may be initiated by radical or ionic initiators or catalysts and may be carried out in emulsion, suspension, bulk or solution polymerisation systems.

In one procedure, the polymerisation is carried out in bulk, the monomer mixture

together with the catalyst and, if required, a suitable cross linking agent, being polymerised in a sealed vessel. Suitable cross linking agents include diesters of unsaturated aliphatic carboxylic acids, and particularly the glycol diacrylates, such as for example ethylene glycol dimethacrylate. In bulk polymerisation a major factor governing the possible range of compositions is the solubility or compatibility of the carboxylic acid amide in the mixture of the other components, and it has been found that the addition of a monoester of an unsaturated carboxylic acid as previously described can increase the solubility or compatibility of the amide. The solid copolymer produced by the reaction may be machined into the shape of the desired article.

In an alternative procedure the polymerisation may be carried out in solution in a non-hydroxylic organic solvent, such as for example dioxan, dimethylformamide or tetrahydrofuran. Preferably the solution polymerisation is carried out in a medium which is a solvent for the monomers and for the copolymer. After reaction the copolymer may then be precipitated, for example by pouring the reaction mixture into a liquid which is a non-solvent for the copolymer.

The polymerisation reaction mixture may contain up to 1% by weight of a polymerisation catalyst, for example benzoyl peroxide, azobisisobutyronitrile, or lauryl peroxide.

The polymerisation may be carried out at a temperature of from 50°C to 120°C or even higher, but preferably the polymerisation temperature is within the range of from 60 to 70°C. Reaction is complete in from half an hour to 24 hours, depending upon the temperature, the amount of catalyst, the relative proportions of the monomers and the nature of any solvent present.

After polymerisation the copolymer may be treated to remove any residual monomer, solvent or initiator, washed and dried under vacuum.

According to the invention the polymer produced by the polymerisation reaction is preferably substantially linear and may thus be moulded in its non-hydrated state into the final shaped article. It is desirable that the polymer should be a substantially linear thermoplastic at least prior to the moulding operation since this enables the polymer to undergo viscous flow under the action of heat and pressure above its glass transition temperature and permits the use of compression or injection moulding techniques. In order that the copolymer should be able to undergo viscous flow it should contain on average not more than one cross link every 50 repeating polymer units, and preferably not more than one cross link every 100 polymer units. In certain cases however, it may be desirable to increase the mechanical strength of the shaped article by introducing a small number of cross links into the polymer,

and this may conveniently be done during the moulding operation by including a small quantity, for example up to 5% by weight of the total copolymer, of an appropriate cross linking agent into the copolymer or by including a like amount of the total monomer mix of a monomer such as a dimethacrylate which can itself cross link under the moulding conditions. The proportion of cross links introduced into the polymer will usually be quite small, preferably one every 10 to 200 repeating polymer units on average and most preferably one every 60 to 100 polymer units.

In one method of processing, the polymer is first cast into a sheet, for example by solution casting, and then individual shaped articles are compression moulded from the sheet. Usually the moulding temperature is from 120 to 300°C and the moulding pressure from 10 lbs. per sq.in. to 20 tons per sq.in. As previously mentioned it is at the moulding stage that any cross linking agent present in the polymer will become activated. The cross linking agent may be added immediately prior to the moulding step, but preferably, in the case of the sheet, the cross linking agent is added either to the monomer mixture prior to the polymerisation or to the casting solution. The cross linking agent may be one that does not take part in a vinyl polymerisation, for example succinic anhydride, pyromellitic dianhydride, 1,2,3,4-butane tetracarboxylic acids dianhydride, phthaloyl chloride, or a diepoxide, in an amount of up to 5% by weight of the total monomer mix, preferably from 0.01 to 1.0% by weight, or alternatively it may be a curing agent for latent cross linkable vinyl groups included in the polymer chain. The addition of a small amount, for example, 2% by weight of the total monomer mix, of a peroxide such as, for example, di-cumyl peroxide, provides a curing agent which cross links such latent sites on the polymer when the material is compression moulded. Care should of course be taken that the cross linking agent is not activated by the processing conditions prior to the compression moulding stage.

In an alternative procedure, the copolymer, in powder form, may be directly compression moulded into the appropriate article using moulding conditions within the range specified previously.

Finally the shaped article is immersed in water or an aqueous medium until equilibrium is reached. The quantity of water absorbed by the copolymer depends on the nature of the copolymer and its structure but usually the copolymer should contain from 72% to 80% by weight of water (determined by repeated weighing at 20°C).

The polymeric materials of the present invention have a freely wettable surface and are particularly suitable for the production of contact lenses. They may be made optically clear and have good permeability to oxygen

and carbon dioxide. The oxygen permeability of the plastic materials is usually greater than 100×10^{-10} cc.mm.cm.⁻² sec.⁻¹ cm. Hg.⁻¹ and in some cases may be as high as 200 to $1,000 \times 10^{-10}$ cc.mm.cm.⁻² sec.⁻¹ cm. Hg.⁻¹.

Copolymers in accordance with the invention that are capable of swelling in water to form hydrogels are particularly preferred for contact lens use. These polymers will normally contain in the hydrogel structure up to 80% by weight of water.

In addition, the polymeric material may be used for prosthetic implants within the body, for example, blood vessels, artificial ureters, and artificial breast tissue, and membranes intended to come in contact with body fluids (but outside the body), for example membranes for kidney dialysis and heart/lung machines, swabs, nappy liners, wound dressings and similar applications.

The invention is illustrated by the following Examples:

EXAMPLE 1

The following purified and inhibitor free monomers are thoroughly mixed in the quantities indicated at about 60°C to ensure that all the acrylamide is dissolved:

Acrylamide	35 parts (molar)	95
2-Hydroxypropyl Acrylate	55 parts	
N-Vinyl Pyrrolid-2-one	10 parts	

The reactants are poured into lengths of polyethylene tubing sealed at one end. The system is then purged with nitrogen and sealed. The sealed tubes are placed in a water bath at 60°C for 72 hrs. and then post-cured for 24 hrs. in an oven at 90°C. The polyethylene tubes are cut open to release the polymer rods. From the resulting rod an optically clear disc can be obtained. The polymer has an equilibrium water content of 72% by weight.

EXAMPLE 2

The following formulation is polymerised as described in Example 1:

Acrylamide	55 parts (molar)	110
2-Hydroxypropyl Acrylate	20 parts	
NVinyl Pyrrolidone	30 parts	

From the resulting rod an optically clear disc can be obtained. The polymer has an equilibrium water content of 78% by weight.

WHAT WE CLAIM IS:

1. Polymeric material suitable for use in biomedical applications and in the form of a hydrogel containing units derived from:—

- (i) a hydroxyl substituted olefin and/or a hydroxyl substituted unsaturated aliphatic ester;
- (ii) an amide or an unsaturated aliphatic carboxylic acid; and
- (iii) an unsaturated lactam.

the hydrogel having an equilibrium water content of at least 72% by weight.

2. Polymeric material according to claim 1

wherein the hydrogel also contains units derived from (iv) an unsaturated aliphatic carboxylic acid and/or a mono-ester thereof.

3. Polymeric material according to Claim 1
5 or 2 in which (i) comprises a hydroxyl substituted unsaturated aliphatic ester.
4. Polymeric material according to Claim 3,
10 in which the hydroxyl substituted unsaturated aliphatic ester is an ester of acrylic or methacrylic acid and a dihyric alcohol.
5. Polymeric material according to any pre-
ceding Claim, in which (ii) comprises an amide
of acrylic acid or methacrylic acid.
6. Polymeric material according to any pre-
15 ceding Claim, in which (iii) comprises a N-Vinyl lactam.
7. Polymeric material according to Claim 6,
in which the N-vinyl lactam is N-vinyl pyrro-
lidene.
- 20 8. Polymeric material according to any of
Claims 2 to 7, in which (iv) comprises meth-
acrylic acid or a higher homologue thereof.
9. Polymeric material according to any of
Claims 2 to 8, in which (iv) comprises an ester
25 of acrylic or methacrylic acid.
10. Polymeric material according to any
preceding Claim, that comprises a copolymer of
from 5 to 70 mole % of (ii) and from 5 to 50
mole % of (iii) and (iv) (where present),
percentages being relative to the total copolymer. 30
11. Polymeric material according to Claim
10 that comprises from 5 to 45 mole % of (ii).
12. Polymeric material according to any
preceding Claim, that is cross linked to the
extent of one cross link to every 10 to 200 35
polymer units.
13. Polymeric material according to any
preceding Claim, in which the hydrogel has an
equilibrium water content of up to 80% by
weight. 40
14. Polymeric material according to any
preceding Claims, in which the hydrogel con-
tains units derived from 2-hydroxypropyl acry-
late, acrylamide, N-vinyl pyrrolid-2-one and
methacrylic acid. 45
15. Polymeric material substantially as des-
cribed in either of the Examples.
16. A contact lens formed from a polymeric
material according to any preceding Claim. 50

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